REMARKS

Upon entry of the foregoing amendment, claims 2-12, 16-22, 25, 26 and 28-38, 42, 43, and 45-52 are pending in the application, with claims 1, 13-15, 23-24, 27, 39-41 and 44 canceled without disclaimer of, or prejudice to the matter as originally claimed. Although claims 1-27 have been withdrawn by the Examiner under 35 U.S.C. § 121, Applicant has amended method claims 2-12, 16-22, 25 and 26 to include the limitations of the product claims.

Currently, claims 28-52 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly adding new matter. Also, claims 28-52 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not complying with the written description requirement and the enablement requirement. Also, claims 28-52 stand rejected as allegedly being obvious under 35 U.S.C. § 103. Claims 28-52 and the specification are objected to for the use of the phrase "biological equivalent." Also, claim 50 is objected to for using the language mitochondrial "function."

Claims 28-52 are amended to remove the terms "wild-type" and "biological equivalent thereof." Claims 28-52 are also amended to indicate that the compositions of the present invention are able to treat prostate cancer that includes both androgen responsive and androgen independent prostate cancer cells and that treatment of prostate cancer cells with the compositions of the present invention is more effective than the additive effect of treatment of prostate cancer cells separately with TRAIL and an antiprogestin. Support for the amendment of the claims is found in the specification at page 18, lines 18-27, and Figure 1, describing the synergistic effects of using TRAIL and an antiprogestin. Claim 50, and withdrawn claim 21, are amended to describe that the loss of mitochondrial function comprises a reduction in mitochondrial cytochrome c. Support for this amendment may be found in the specification at page 22, lines 8-14. Other amendments are made to correct typographical errors or to clarify the syntax of the claim language. Also, withdrawn claims 2-12, 16-22, 25 and 26 are amended to describe a method for treating prostate cancer comprising androgen responsive and androgen independent cells by inducing cell death in prostate cancer cells comprising an effective amount of a Tumor necrosis factor α - Related Apoptosis Inducing Ligand (TRAIL) polypeptide comprising the amino acid sequence SEQ ID NO: 1, and an antiprogestin in

a pharmaceutical carrier, such that the TRAIL polypeptide and antiprogestin induce apoptosis in a greater number of the prostate cancer cells than the additive effect of treatment of the prostate cancer cells separately with TRAIL and an antiprogestin. As amended, the withdrawn claims have the same scope as the composition claims. Accordingly, no new matter is added by the amendments to the claims.

Also, the specification is amended to remove the phrase "or a biological equivalent thereof" that was introduced in Applicant's previous amendment and response. Accordingly, no new matter is added by the amendments to the specification.

The Objection to the Claims and Specification is Traversed or Rendered Moot

The Examiner objected to the claims, and to the specification under 35 U.S.C. § 132, for the use of the term "biological equivalent." The phrase "the biological equivalent thereof" has been deleted from the specification and independent claims 28, 30 and 42.

The Examiner also objected to the use of the term mitochondrial "function" in claim 50. Claim 50, and withdrawn claim 21, are amended to describe that treatment of cancer cells with TRAIL polypeptide and Mifepristone is associated with a reduction of mitochondrial cytochrome c in the treated cells.

In view of the amendment to remove and/or replace the terminology objected to by the Examiner, the Applicant respectfully requests that the objections to the claims be withdrawn.

The Rejection of Claim 32 Under 35 U.S.C. 112, First Paragraph, is Traversed or Rendered Moot

The Examiner rejected claims 28-52 for using the terms "wild-type" and "biological equivalent." Thus, the Examiner stated that "[t]he limitation of the 'biological equivalent' of a 'wild type' TRAIL polypeptide comprising SEQ ID NO: 1 claimed in Claims 28-52 has no clear support in the specification and the claims as originally filed." Office Action at page 2. As noted by the Examiner, the Federal Circuit has recently clarified that a molecule, such as a protein or a DNA molecule, may be adequately described without disclosing its complete structure where features common to

the members of the genus are described. *Enzo Biochem, Inc., v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002). Applicant respectfully asserts that the instant specification describes that polypeptides that are biologically equivalent to TRAIL, as such peptide variants of the wild-type TRAIL sequence, may be routinely generated and then evaluated using the assay systems described in Applicant's specification (e.g., Examples 2-10). Still, to facilitate prosecution, and without in any way acquiescing to the Examiner's basis for the rejection, Applicant has removed the terms "wild-type" and "biological equivalent" from the claims. Applicant respectfully asserts that the claims, as amended, do not include new matter, and satisfy both the written description requirement and the enablement requirement under 35 U.S.C. § 112, first paragraph. Thus, Applicant respectfully requests that the rejection of the claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Rejection of the Claims Under 35 U.S.C. 103 is Traversed or Rendered Moot

The Examiner rejected claims 28-44 under 35 U.S.C. 103(a) as being allegedly unpatentable over Bonavida, B. et al., 1999, Oncology 15(4):793-802 (hereinafter "Bonavida"), Yu et al, 2000, Cancer Res., 60:2384-2389 (hereinafter "Yu"), or Gliniak, B., et al., 1999, Cancer Res., 59:6153-6158, (hereinafter "Gliniak"), in view of Fathy El Etreby et al., 2000, The Prostate 42: 99-106 (hereinafter "Fathy El Etreby"), or Kiode, S.S., et al., J. Reproductive Medicine, 1998, 43:551-560 (hereinafter "Kiode").

Applicant again asserts that the Examiner is using hind-sight as a basis for combining the cited references and therefore, has not established a *prima facie* case of obviousness. The Examiner apparently cites Bonavida, Yu, and Gliniak as describing the use of TRAIL to induce apoptosis in tumor cells. The Examiner cites the other two references, Fathy El Etreby and Koide, as allegedly describing that Mifepristone may be used to treat prostate cancer (Fathy El Etreby) or other types of cancer (Koide). Applicant maintains that there is no teaching or suggestion in the cited references that TRAIL and Mifepristone may be combined as a composition to effectively prevent prostate cancer cell growth in cells that are resistant to TRAIL, such that the combination of TRAIL and Mifepristone is more effective than either TRAIL or Mifepristone alone.

Also, Applicant has amended the claims to describe a composition comprising TRAIL and an antiprogestin for the treatment of prostate cancer, where the prostate cancer comprises both androgen responsive prostate cancer and androgen independent prostate cancer, and wherein an effective amount comprises sufficient TRAIL polypeptide and antiprogestin to induce apoptosis in a greater number of the androgen responsive and androgen independent prostate cancer cells than when the TRAIL and the antiprogesterin are applied separately. Support for the amendment of the claims is found in the specification at page 18, lines 18-27, and Figure 1, describing the synergistic effects of using TRAIL and an antiprogestin. Applicant respectfully asserts that there is absolutely no teaching or suggestion in the cited art that an antiprogestin could be combined with TRAIL to induce apoptosis in both androgen responsive and androgen independent prostate cancer cells at levels greater than the additive effects of each agent alone.

First, neither Bonavida, Gliniak or Kiode refer to prostate cancer and thus, do not describe, teach or suggest methods and compositions for the treatment of prostate cancer. Bonavida describes the use of TRAIL to induce apoptosis in human mammary adenocarcinaoma cells, and Gliniak describes that TRAIL can induce apoptosis in several transformed human cells *in vitro*, but does not describe the use of TRAIL in prostate cancer cells. Koide describes the use of Mifepristone to treat cancers other than prostate cancer. It is well known in the field of cancer biology that a treatment that may work for one type of cancer is often ineffective for other types of cancers, and that even within a single cancer type, some cells may be refractory to treatment by a particular agent. Also, designing treatments for prostate cancer is complicated by the fact that prostate cells grow slowly (one reason the disease is seen in older men) and therefore, drugs specifically directed towards inhibiting cell growth that are effective in many other cancers, are not very efficient in treating prostate cancer.

Also, the non-obviousness of Applicant's invention is substantiated in view of the surprising results found by Applicant that: (1) combining TRAIL and an antiprogestin such as Mifepristone is synergistic; and (2) that TRAIL and Mifepristone may be used to induce apoptosis in both androgen responsive and androgen independent prostate cancer cells.

First, Applicant was the first to demonstrate that Mifepristone can sensitize cells to the effects of TRAIL. As described in Applicant's specification, the challenge in prostate cancer is to develop agents that are effective in treating both androgen-sensitive prostate cells and androgen-insensitive prostate cancer cells. Although Yu describes the use of TRAIL to induce apoptosis in androgen independent cancer cells, Applicant was the first to discover that Mifespristone can increase the efficacy of TRAIL in inducing apoptosis in those prostate cancer cells that are resistant to the apoptic effects of TRAIL. For example, as taught by Applicant's specification, LNCaP androgen responsive prostate cells are not responsive to TRAIL. Treatment of such prostate cancer cells with TRAIL does not result in a significant increase in apoptosis (Figure 1A and 1C of Applicant's specification). Thus, as shown in Figure 1 treatment of LNCaP cells with 400 ng/ml TRAIL does not alter cell survival significantly. Also, such cells were not sensitive to Mifepristone (see e.g., Figure 1A and 1C). However, treatment of LNCaP cells with Mifepristone followed by TRAIL results in a significant decrease in cell survival (Figure 1A and 1C).

Also, as shown by Applicant's specification, the combination of Mifepristone and TRAIL results in effects that are more than additive, but that display synergy. Thus, as shown in Figure 1A , for LaNCaP cells at 16 h, the combination of Mifepristone plus TRAIL results in a substantially greater reduction in survival (down to 40% survival or 60% cell death) than the individual reduction for TRAIL (down to 80% survival or 20% cell death) plus Mifepristone (> 95% survival or < 5% cell death). Similar results are seen for the measurement of apoptosis using the Apoptosense assay (Figure 1C) that measures cytokeratin exposed as a result of apoptosis. Thus, after 16 hours, the measured levels of cytokeratin 18 for the combination treatment of TRAIL and Mifepristone was about 2.9 units (U) cytokeratin 18 per μg total protein, whereas individually, TRAIL resulted in about 0.6 U/μg and Mifepristone resulted in about 1 U/μg.

Applicant respectfully asserts that there is nothing in the cited references that teaches or suggests the surprising synergy exhibited by the combination of TRAIL and Mifespristone, or that the combination of TRAIL and Mifespristone would be effective to treat prostate cancer cells that are refractory to TRAIL alone. For at least the above

reasons, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

Rejoinder of Withdrawn Claims

Withdrawn process claims that depend from, or otherwise include all of, the limitations of an allowable product claim may be rejoined in accordance with the provisions of MPEP § 821.04, and such amendments will be entered as a matter of right if presented prior to allowance. Applicant has amended claims 2-12, 16-22, 25 and 26 to include the limitations of the product claims. Applicant respectfully asserts that as amended, the withdrawn claims are in a form suitable for immediate allowance, and request reentry of the amended method claims 2-12, 16-22, 25 and 26 into the application.

CONCLUSION

In view of the foregoing amendment and remarks, each of the claims remaining in the application is in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections. The Examiner is respectfully invited to telephone the undersigned at (336) 747-7541 to discuss any questions relating to the application.

Respectfully submitted,

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